REMARKS

I. Status of the claims and application

Claims 26-83, 85, and 93, 96-112, 117-124, 126, 135, 136, and 138 are pending. Claims 26-83 and 85 are withdrawn from consideration. Claims 1-25, 84, 86-92, 94, 95, 113-116, 125, 127-134, 137 were canceled previously, without prejudice or disclaimer. Applicants reserve the right to pursue any of the canceled subject matter in one or more continuing applications. Claims 93, 96-112, 117-124, 126, 135, 136, and 138 are under examination.

Claims 93 and 117 are amended to clarify that SC20 is actually contained with the chicken DT-40 cell; and that the Accession Number FERM BP-7583 references the deposited chicken DT-40 cell.

The specification is similarly amended at page 65 to clarify the same and to also relate the full name and address of the depository: "...SC20, which is retained within the chicken DT-40 cell that bears the Accession Number FERM BP-7583, wherein the DT-40 cell was deposited under that Accession Number in the International Patent Organism Depository denoted as the National Institute of Advanced Industrial Science and Technology, located at the Advanced Industrial Science and Technology (Tsukuba Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki, Japan)."

II. The claimed recombinant chromosome is made from non-essentially chromosomal starting material, which is fragmented by a non-irradiative method

Claims 93, 96-112, 117-124, 135, 136, and 138 are rejected as allegedly non-enabled, under 35 U.S.C. § 112, first paragraph. The Examiner questions whether the chromosomal "starting material" from which the claimed fragments are derived can be obtained by a repeatable method (office action at page 8).

According to the Examiner, the examples "appear to use a particular clone, which is an essential starting material" to produce the claimed fragments (page 7). As she understands it, the microcell-mediated chromosome transfer (MMCT) method that is used to create that [6-1] clone causes spontaneous fragmentation (page 4). In her view, therefore, the 6-1 clone itself remains unobtainable, regardless of the site-specific techniques that are performed on it subsequently, thereby to generate a desired sub-fragment.

This is not true. The determinative issue is not whether the specification makes it possible to later obtain an identical copy of any specific clone. Rather, it is whether the specification provides a repeatable and controlled method for obtaining a chromosome fragment that contains an antibody locus.

Put simply, Applicants' specification enables one to join chromosome fragments, at least two of which contain antibody loci, to make the claimed recombinant chromosome. The fragments can be produced spontaneously or non-spontaneously.

Applicants do not, therefore, wish to lose sight of the context of the present invention by focusing solely on one or more examples. Hence, an exhaustive discussion of how Applicants derived these *particular* clones is only tangentially relevant to the fact that the specification is enabling for a reproducible method of obtaining a chromosome fragment that contains an antibody locus.

Applicants acknowledge the Office's request for clarification, however, regarding the "essential starting material" and take this opportunity to clarify the record in response to those most recent concerns.

Applicants also take this opportunity to thank Examiner Ton for inviting Applicants to submit a Rule 132 Declaration to corroborate and further clarify the methods by which the claimed recombinant chromosome is made. See the office action at page 6. Accordingly, Applicants submit herewith a Rule 132 Declaration by co-inventor, Dr. Kazuma Tomizuka.

Dr. Tomizuka's declaration describes, among other specifics, how the claimed chromosome is made (see, for example, paragraph 10 of the declaration) and the origins of the material that was used to make the claimed chromosomes (paragraph 14).

The following details cover those issues and makes clear that the method for making the claimed recombinant chromosome is reproducible and that the genetic material that is used in that method is not "essential starting material."

(a) A9/#22, A9/#22neo, and clone 6-1 are essentially identical to each other

Three observations should help to confirm that the specification is enabling for the claimed recombinant chromosome:

(i) Clone 6-1 is essentially identical to A9/#22. Clone 6-1 is resistant to puromycin and G418 neomycin. See Example 26 at p. 149. The A9/#22 cell is the ancestral cell of 6-1, but is resistant to only G418 neomycin.

(ii) A9/#22 of Example 2 is the same as "A9/#22neo" of Example 82. The "neo" designation emphasizes the presence of the G418 neomycin resistant gene on chromosome #22. While "A9/#22" lacks that specific designation, the A9/#22 clone also carries the G418 resistant gene. See Example 1 at p. 91, line 4 to p. 92, line 8.

(iii) The G418 neomycin and puromycin resistance genes are used as selectable markers to identify cells that are cultured on neomycin- and puromycin-containing substrates.

(b) An intact human chromosome #22 was transferred from a human cell to a mouse cell via non-irradiative MMCT and "A9/#22" cells were identified that contained an intact chromosome #22

Applicants produced A9/#22-neomycin resistant cells by MMCT without irradiation. They (1) integrated a G418 resistant gene into chromosome #22 of human normal fibroblast cells (HFL-1); (2) fused those cells to mouse A9 cells via MMCT; (3) cultured those fused cells on G418 selective media; and (4) identified G418 resistant cells.

The resistant cells were screened by PCR and fluorescence *in situ* hybridization (FISH) to identify those that contained an unfragmented human chromosome #22. Applicants called these cells A9/#22. See pp. 99-102.

Example 2 describes this sequence of events and details treatment of non-irradiated cells and irradiated cells – it reports that clones E14/#22-9 and E14/#22-10 were created by fusing "nonirradiated" microcells with ES cells. Each clone was found to retain an essentially intact chromosome #22. See p. 101, line 27 to p. 102.

Example 82 similarly describes how chromosome #22 of A9/#22neo cells was transferred into chicken DT40 cells, and how one resultant clone, "52-18," was found to contain an intact human chromosome #22 (p. 274, lines 2-4).

Accordingly, it is an error for the Examiner to conclude that the examples, especially Example 2, are drawn solely to clones "generated by irradiation of the A9/#22 microcells" (p. 5 of the office action). The G418-resistant chromosomes of the A9/#22 and A9/#22neo cells described in Examples 2 and 82 are not fragmented.

(c) Unfragmented chromosomal #22 was site-specifically truncated and ligated to other fragments to produce the claimed recombinant chromosome

The unfragmented chromosomal #22 "starting material" was specifically cleaved at its LIF gene locus via telomere truncation. The desired fragment then was ligated to a chromosome #14 fragment to produce the human artificial chromosome, "λHAC." See Examples 83, 93, and 97.

Similarly, Applicants constructed the human artificial chromosome "κHAC" by ligating together specific fragments obtained from intact copies of chromosomes #2 and #14.

By adopting this overall approach in various experiments, Applicants were able to demonstrate they could routinely obtain mouse A9 cells that contained intact copies of human chromosome #2, #4, #14, and #22; and that those intact chromosomes could be truncated at any desirable locus to generate fragments for co-ligation.

III. Claims 93 and 117 are not indefinite

The Examiner alleges claims 93 and 117 are indefinite under 35 U.S.C. § 112, second paragraph because "it is unclear what the Accession Number refers to" and because the "it is unclear what the human chromosome #14 centromere of SC20 is" (office action at page 9).

Applicants clarify in both claims 93 and 117 that SC20 is contained with a chicken DT-40 cell denoted by the recited Accession Number and that SC20 contains the centromere of human chromosome #14. Applicants believe that this clarification resolves any issues concerning the alleged indefiniteness of the prior claim. Accordingly, Applicants respectfully request withdrawal of this rejection.

VI. Conclusion

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

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